

Duplicate skin prick testing in the assessment of food allergy

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Clinical Implications

- Duplicate skin prick tests may provide additional benefit in the diagnosis of food allergy and should be considered in the evaluation and management of patients with food allergy, especially in anticipation of oral food challenge.

TO THE EDITOR:

Food allergy is a significant cause of morbidity and mortality, particularly in the pediatric population.¹⁻³ Skin prick testing to specific foods is important for the accurate diagnosis of food allergy, as well as for assessing the likelihood of having outgrown a food allergy and/or being a candidate for undergoing oral food challenge (OFC).⁴ Duplicate skin prick test (dSPT) is one method to potentially reduce false-negative SPT results and safely predict successful OFCs. Although a previous study of inhalant and food allergen duplicate testing did not show significant discordance between duplicate test results, we sought to reassess the utility of dSPTs in children using our current SPT device and allergen extract preparations given its current use in our clinic. Some of our clinic providers use dSPTs in situations of clinical

uncertainty, whereas others routinely use dSPTs because of anecdotal observation that it increases test reliability.

We performed a retrospective analysis of dSPTs to common food allergens at Boston Children's Hospital. We included all results from patients who underwent dSPTs between October of 2009 and July of 2016 as well as the corresponding specific IgE levels between October of 2008 and July of 2017, within 1 year of dSPTs. All SPTs were performed using the Multi-Test cassette skin testing device by Lincoln Diagnostics, Inc, in a standardized fashion. The Multi-Test device was more than 97% sensitive and specific in previous trials using histamine and saline controls, and we favor it for ease of use with children owing to ability to apply 8 tests simultaneously.⁵ Commercially prepared food extracts were used for all tests (cow's milk, egg, and peanut were obtained from GREER, and other extracts were obtained from 1 of the following: GREER [Cambridge, MA], Lincoln Diagnostics [Decatur, IL], ALK-Abello [Hørsholm, Denmark], and Allergy Laboratories, Inc [Oklahoma City, OK]). Histamine and normal saline controls were also placed per routine. Specific IgE levels were measured using the ImmunoCAP assay.

Over the 7-year study period, 7132 dSPTs to foods were performed on 1067 patients for various food allergens (Table I). Results were first analyzed in aggregate, with positive reactions defined as wheal of greater than or equal to 3 mm plus flare of greater than or equal to 4 mm.⁶ Discordant results were defined as 1 positive and 1 negative SPT result. With this allergen nonspecific cutoff, 13.5% (95% CI, 12.7%-14.3%) of the dSPTs were discordant, with a range of variability of 1 mm to 25 mm difference in wheal size between the 2 tests. Kappa statistic was 0.72 (95% CI, 0.70-0.74; McNemar test $P < .001$). Among

TABLE I. Duplicate skin prick testing (7132 dSPTs from 1067 children)

Variable	Total, n	Both negative, n (%)	Both positive, n (%)	Discordant results, n (%)	Discordant results, 95% CI
All tests	7132	3797 (53.2%)	2373 (33.3%)	962 (13.5%)	12.7%-14.3%
Age category (y)					
<2	604	434 (71.9%)	123 (20.3%)	47 (7.8%)	5.8%-10.2%
2-5	2172	1246 (57.4%)	619 (28.5%)	307 (14.1%)	12.7%-15.7%
6-11	2715	1331 (49.0%)	993 (36.6%)	391 (14.4%)	13.1%-15.8%
12-21	1641	786 (47.9%)	638 (38.9%)	217 (13.2%)	11.6%-15.0%
Sex					
Male	4510	2276 (50.5%)	1586 (35.2%)	648 (14.4%)	13.4%-15.4%
Female	2622	1521 (58.0%)	787 (30.0%)	314 (12.0%)	10.8%-13.3%
Location					
Back	3117	1405 (45.1%)	1206 (38.7%)	506 (16.2%)	15.0%-17.6%
Arm	3831	2294 (59.9%)	1107 (28.9%)	430 (11.2%)	10.2%-12.3%
Technicians					
Tech 1	1666	748 (44.9%)	625 (37.5%)	293 (17.6%)	15.8%-19.5%
Tech 2	1155	665 (57.6%)	313 (27.1%)	177 (15.3%)	13.3%-17.5%
Tech 3	1027	589 (57.4%)	322 (31.4%)	116 (11.3%)	9.4%-13.4%
Tech 4	614	389 (63.4%)	158 (25.7%)	67 (10.9%)	8.6%-13.7%
Tech 5	434	222 (51.2%)	151 (34.8%)	61 (14.1%)	10.9%-17.7%
Others	2236	1184 (53.0%)	804 (36.0%)	248 (11.1%)	9.8%-12.5%

Positive reactions defined as wheal ≥ 3 mm with flare of ≥ 4 mm.

Discordant results defined as 1 positive and 1 negative.

P value based on the McNemar test.

the discordant duplicate tests, 44.6% had a 3- to 4-mm difference, 31.1% had a 5- to 9-mm difference, 5.3% had 10- to 14-mm difference, and 2.8% had a difference of 15 mm or more.

Discordance of the dSPT was observed among males (14.4%; 95% CI, 10.8%-13.3%) and females (12.0%; 95% CI, 10.8%-13.3%). Discordance occurred both when testing was done on the back (16.2%; 95% CI, 15.0%-17.6%) and the arm (11.2%; 95% CI, 10.2%-12.3%). When we evaluated the within-individual correlation on the basis of mixed-effects logistic regression model, the intraclass correlation coefficient (ICC) was 0.11 (95% CI, 0.08-0.15). The low ICC suggests that the same individual with discordant results for an allergen is not more or less likely to have discordant results for other allergens. We further analyzed results by technician performing the assays, to determine whether this was a major factor in discordance and reproducibility; the discordance ranged from 10.9% to 17.6%. Scatter plots of the wheal size between duplicate tests are shown in Figure 1. Concordance correlation coefficient was 0.82 (95% CI, 0.81-0.82).

95% positive predictive value (PPV) cutoffs specific to food allergens based on failed oral challenges have been previously reported. Therefore, we subanalyzed dSPT for the most commonly tested food allergens of peanut ($n = 451$), egg ($n = 542$), and cow's milk ($n = 354$) using PPV reference ranges

from the literature.^{4,7,8} For peanut, the 95% PPV wheal size was 4 mm or more for children younger than 2 years and 8 mm or more for children 2 years or older; for egg, 95% PPV wheal size was 4 mm or more for infants younger than 1 year, 5 mm or more for children younger than 1 to 2 years, and 7 mm or more for children 2 years or older; and for cow's milk, 95% PPV wheal size was 6 mm or more for children younger than 2 years and 8 mm or more for children 2 years or older. On the basis of these cutoffs, we found significant dSPT discordance for peanut (12.6%; 95% CI, 8.0%-13.9%), egg (15.3%; 95% CI, 12.4%-18.6%), and cow's milk (10.4%; 95% CI, 7.5%-14.1%).

We then investigated the correlation of sIgE levels with dSPT results. We reviewed the data set of dSPT and identified all patients who had sIgE tested within 1 year of the dSPT ($n = 4309$). We found that 59.9% of discordant tests corresponded with a positive specific IgE (≥ 0.35), whereas 40.1% corresponded with a negative sIgE. The wheal size discordance was correlated with positive sIgE (P for trend $< .001$). When the wheal size discordance was 1 to 2 mm ($n = 66$), sIgE was positive 56.4% of the time, whereas when discordance reached 15 mm or more ($n = 19$), the percent of positive sIgE was 90.5%.

Looking at the most extreme examples of discordance, for those with 15 mm or more difference in wheal size, sIgE levels

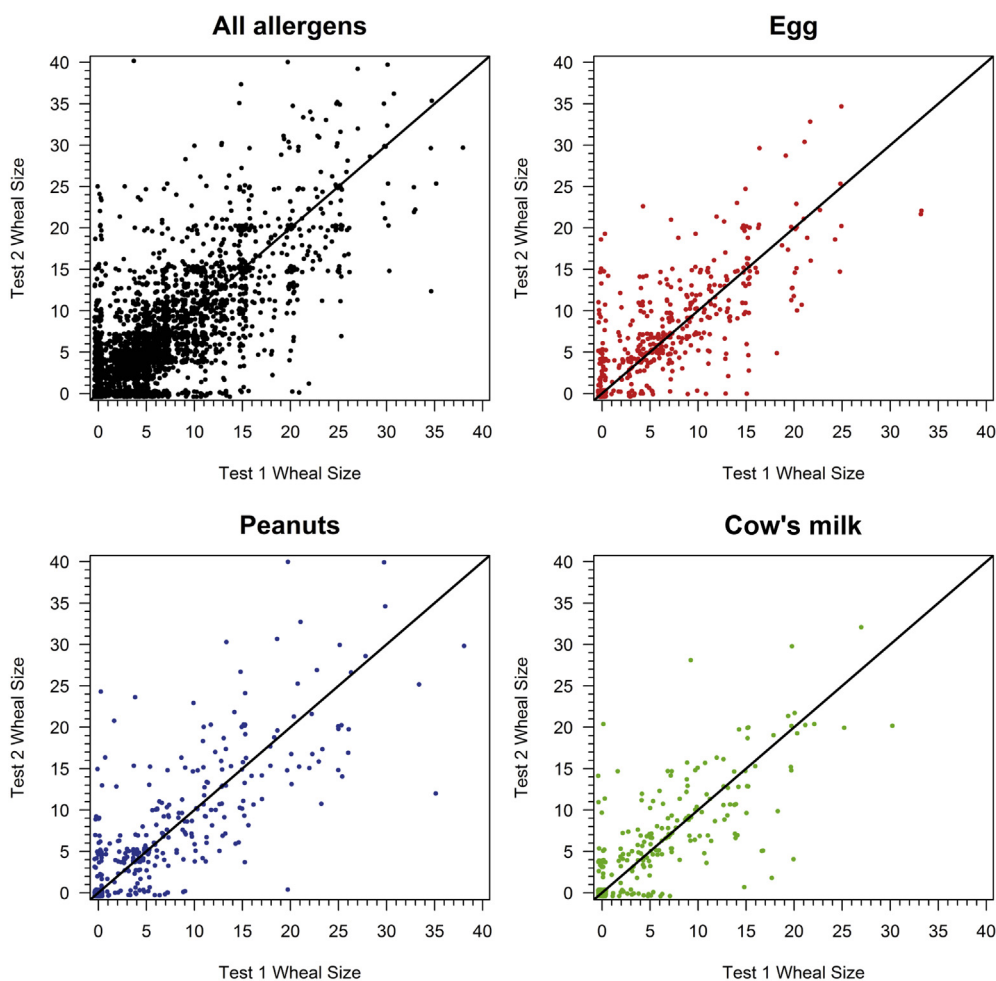


FIGURE 1. Wheal size comparison among 7132 dSPTs with test 1 on x-axis and test 2 on y-axis.

were elevated in all but 2 tests. This suggests that most often extremely discordant testing occurs in the setting of a test that is a technical error or failure to correctly place 1 of the 2 tests. The use of dSPT in this scenario improves diagnostic accuracy and pretest diagnosis before patient selection for OFC, which could lead to improved outcomes and fewer systemic reactions from failed OFCs.

Overall, the degree of discordance in skin prick testing reported here suggests that duplicate skin testing could be helpful in improving the accuracy of food allergy diagnosis as well as more reliably identifying appropriate candidates for undergoing and passing OFCs, thereby minimizing potentially severe reactions from failed challenges. Our data suggest that dSPTs might be useful for skin testing to a wide range of foods in all pediatric age groups. Further studies are needed to determine to what extent dSPTs can decrease severe allergic reactions to foods, from inaccurate diagnoses or failed food challenges.

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